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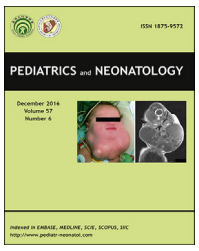

ORIGINAL ARTICLE

Efficacy of Medical Treatment for Infantile Hypertrophic Pyloric Stenosis: A Meta-analysis

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atropine;
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Background: Infantile hypertrophic pyloric stenosis (IHPS) is a common disease in infancy. Pyloromyotomy is universally considered the treatment for IHPS; however, oral or intravenous atropine has been reappraised for the treatment of IHPS in the past 20 years. We investigated the efficacy of atropine in the medical management of IHPS by using meta-analysis and investigated the sonographic changes of the pyloric canal, as well as the efficacy and adverse effects of atropine.
Methods: Information was retrieved from PubMed, Ovid, and MEDLINE. The efficacy and adverse effects of atropine treatment for IHPS were reviewed using the standard process of meta-analysis.
Results: Eleven articles were obtained. Five reports showed that 77 of 110 (70%) infants who were administered oral atropine benefitted by the induced remission of IHPS. Six reports showed that 288 of 345 (83.5%) patients who were treated initially with intravenous atropine then changed to oral atropine showed beneficial effects and had no serious side effects. Time to pyloric muscle normalization ranged from 5 weeks to 15 months.
Conclusion: The study results indicate that atropine is a possible alternative treatment for IHPS, particularly in infants with major concurrent disease, and is safe without obvious side effects.

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1. Introduction

Infantile hypertrophic pyloric stenosis (IHPS) showed a frequency of 3.9/10,000 live births between 1996 and 2004 in Taiwan.[1] The incidence declined to 3/10,000 live births in 2007 in Taiwan.[2] It is the most common cause of vomiting that requires surgical intervention in infants.[3] IHPS is an abnormal hypertrophy of the muscle of the pylorus. Pyloromyotomy, introduced by Dufur and Fredet[4] and Fredet[5] in 1908 and Ramstedt[6] in 1912, has become the first choice of treatment, as effective surgical intervention can easily be performed with minimal complications and rare mortality. In 1955, Corner[7] reported on medical treatment using methyl scopolamine nitrate. A group of workers from Osaka, Japan, reported a new regimen using intravenous (IV) methyl atropine nitrate since 1996[8]; thereafter, many studies have discussed the positive effects of atropine for treating IHPS. However, the sample size has been relatively small. Thus, we reviewed all published studies in a meta-analysis to assess the course and outcome of IHPS managed with atropine.

2. Materials and methods

2.1. Data sources

This search covered the period from January 1980 through March 2015. Data were independently extracted by the first two investigators and then cross-checked by all of the investigators to avoid any errors. The effects of medical treatment for IHPS were identified from PubMed, MEDLINE, and Ovid Medline using the following subject headings (MeSH) and text word terms: "(Infantile) hypertrophic pyloric stenosis, medical treatment, atropine therapy."

The diagnostic criteria for IHPS were repeated projectile vomiting, and pyloric muscle thickening $\geq$3—4 mm and pyloric canal length $\geq$14—18 mm on ultrasonography.

The selection criteria were as follows: (1) pediatric studies; (2) definite diagnosis of hypertrophic pyloric stenosis in infants using definite diagnostic standards; and (3) experiments analyzing the curative effect of atropine for pyloric stenosis. Case reports were excluded. The quality of each paper was evaluated using the modified Jadad scale[9] based on the adequacy of randomization, blinding, and follow up, with a maximum score of 8 points.

For each study, the date of publication, sample size, patient characteristics, treatment method, side effects, and outcomes were recorded. Successful treatment was defined as patients free from vomiting and steady weight gain.

2.2. Statistical analysis

Data for the successful proportion of medical treatment for IHPS in several studies covering the study period were pooled. The degree of heterogeneity among these studies was shown using the Q statistic and I^2 statistic. If the p value of the Q statistic was smaller than the significant level or if I^2 was >40%, then there was heterogeneity among the studies and the proportions were pooled using the random effect model. If there was homogeneity among studies, the fixed effect model was used to pool proportions. Significance was set at 0.05. Sensitivity analysis was conducted to explore the effect of excluding outliers on the pooled estimate. The funnel plot of the logit event rate against the standard error was assessed for publication bias. In addition, we reanalyzed the data by excluding studies with poor quality (modified Jadad score, $\leq$3). Formal statistical testing included an adjusted rank correlation test and a regression asymmetry test.[10,11] Meta-analysis was performed using the software Comprehensive Meta-Analysis (version 2.2.064; Biostat, Englewood, NJ, USA; 2005).

3. Results

Twelve articles[8,12—22] were obtained in the search (Figure 1). Table 1 summarizes the key characteristics of the 12 articles. Among them, the report of Kawahara et al[19] in 2005 included the same study participants recruited in the report of Kawahara et al[15] in 2002. As such, we excluded the study of Kawahara et al[15] published in 2002. Overall, a total of 11 studies were enrolled in this meta-analysis study. Three studies used oral atropine alone, whereas six studies used IV atropine initially, then substituted oral atropine. In two studies, atropine was given orally, then intravenously if ineffective. Oral atropine was given at an initial dose of 0.05 mg/kg/d and increased to a maximum dose of 0.1 mg/kg/d. The dose of IV atropine was started at 0.04—0.06 mg/kg/d and increased by 0.01 mg/kg/d until vomiting ceased. The IV atropine was then changed to oral atropine at twice the effective IV dose.

Treatment was discontinued under the following conditions: ultrasonography showed normalization of pyloric muscle thickness; passage of food through a wide channel on ultrasonography; the patient started gaining weight; vomiting ceased and then resumed for 2—3 weeks; or vomiting ceased and oral atropine was continuously used until the age of 10 weeks.

Five reports showed that in 110 patients receiving oral atropine, 77 (70%) patients showed beneficial effects in that treatment induced remission of IHPS whereas three cases converted to IV atropine. Six reports with a total of 345 patients who received IV atropine followed by oral atropine showed IHPS remission in 288 (83.5%) patients. The mean duration of medical therapy was 24—63 days.

The patients treated successfully with atropine showed steady weight gain. Three studies showed a mean weight gain of 17—30 g/d during the admission period in the groups with successful atropine therapy.[15,16,21] The body weight range on admission was from below the 3rd to the 25th percentile, and after 1 month of IV atropine treatment, the body weight range was from the 10th to 75th percentile in the study of Huang and Su.[16] Kawahara et al[15] reported a significant increase in body weight during atropine treatment by comparing body weight at 6 months of age with that at presentation. The adverse effects related to the use of IV atropine included flushing (7/184, 3.8%), tachycardia (14/184, 7.6%), and transient increase in serum alanine aminotransferase (ALT) level (12/184, 6.5%). There was no adverse effect related to the use of oral atropine.

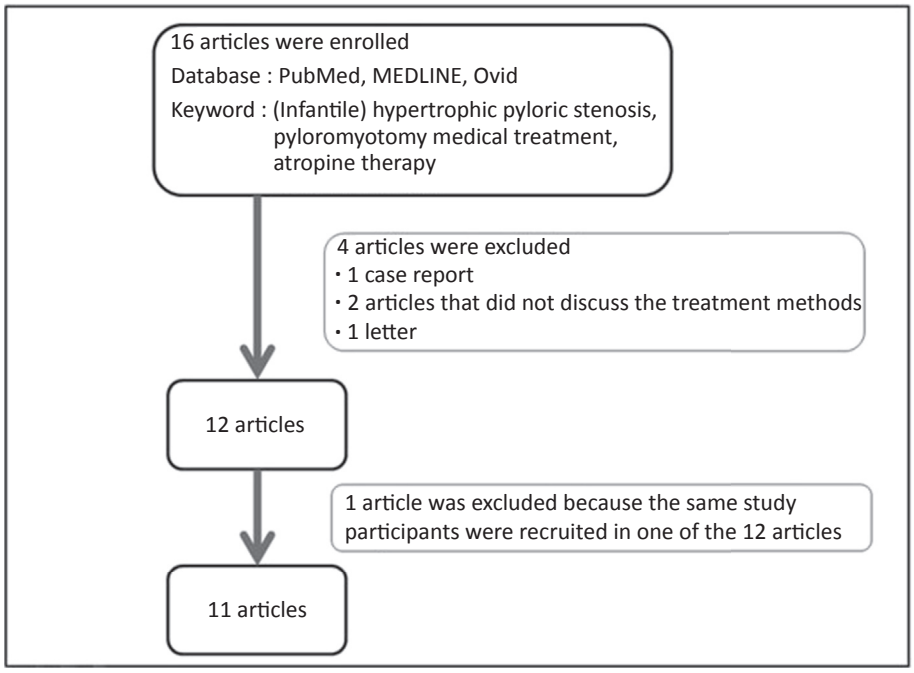

Figure 1 Study selection process. The flowchart summarizes the selection of studies including numbers and reasons why some studies were excluded.

In the present study, I^2 was 70.2% and the p value of the Q statistic was <0.001, which indicated significant variability among studies. The random effect model was selected to pool the proportions to estimate the overall proportion and the forest plot of the 11 included trials (Figure 2). The overall proportion of effective treatment with atropine was 0.806 [95% confidence interval (CI), 0.708—0.876; $p < 0.01$]. Ten trials had similar proportions to the overall proportion and a strong tendency for successful treatment. Only one trial showed ineffective treatment (proportion, 0.318). The study by Huang and Su[16] had the largest variance and lowest pooling weight in the meta-analysis procedure (95% CI, 0.378—0.995).

A sensitivity analysis was performed to explore the effect of outliers on the pooled estimate by removing the study of Kawahara et al,[15] who reported a success rate two

Table 1 Demographic data of the 12 studies.

Author	Atropine group (successful cases/total cases)	Age at admission weeks)	Birth weight (g)	Weight at admission (g)	Days to arrest vomiting	Hospital stay (days)	Publish date
Nagita A.[8]	21/23	7.8 (mean)	NA	3658 (mean)	5.1 (mean)	NA	1996
Yamataka A.[12]	11/14	11.4 (mean)	3046 (mean)	3622 (mean)	NA	NA	2000
Riccabona M.[13]	7/22	6 (mean)	NA	NA	NA	NA	2001
Singh UK.[14]	50/52	NA	NA	NA	NA	NA	2001
Kawahara H.[15,*]	17/19	6.6 (median)	3192 (median)	4043 (median)	NA	13	2002
Huang YC.[16]	5/5	4.4 (mean)	2911 (mean)	4000 (mean)	1.8 (mean)	14.6	2004
Sretenovic A.[17]	18/22	3-12	NA	NA	3.3 (mean)	NA	2004
Singh UK.[18]	11/12	4.1	NA	NA	17.1 (mean)	2	2005
Kawahara H.[19]	45/52	5.7 (median)	2981 (median)	3730 (median)	NA	13 (median)	2005
Meissner PE.[20]	25/33	5.0 (mean)	NA	3860 (mean)	5.8 (mean)	NA	2006
Lukac M.[21]	30/40	3.2 (mean)	NA	3680 (mean)	7 (mean)	8 (mean)	2013
Takeuchi M.[22]	142/180	5.7 (mean)	NA	NA	NA	13.5 (median)	2013

Abbreviation: NA, not available.
* The report by Kawahara H[19] included the same study subjects recruited in the report by Kawahara H[15]. The study of Kawahara H[15] was excluded in this study.

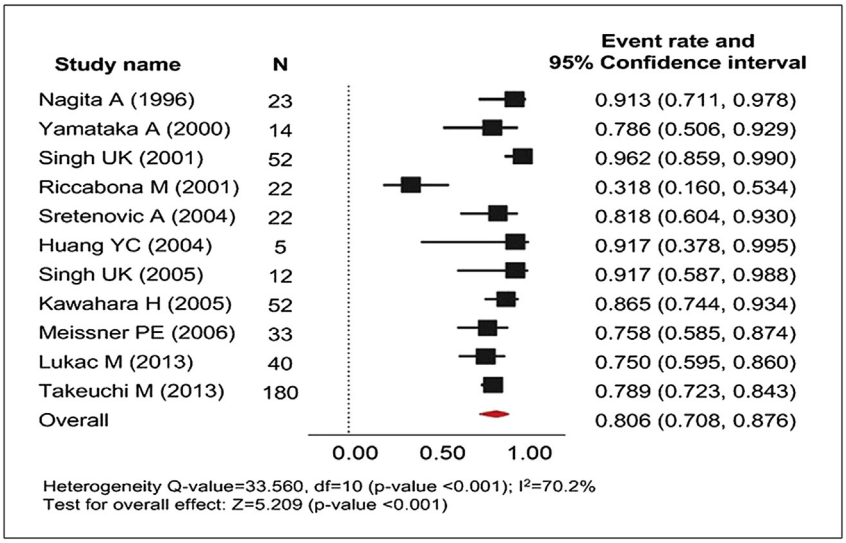

Figure 2 Forest plot of 11 enrolled studies.

times lower than that of the other 10 studies (0.318 vs. 0.750—0.962). After the study was removed, the I^2 value decreased from 70.2% to 23.99%. The summary event rate changed from 0.806 (95% CI, 0.708—0.876) to 0.811 (95% CI, 0.769—0.846). This result was not sensitive to the outlier. In addition, we reanalyzed the data by excluding the low-quality studies, and the result [summary event rate, 0.791 (95% CI, 0.742—0.832); $p < 0.001$; five trials, $n = 319$; heterogeneity, $p = 0.679$) was consistent with that obtained by pooling all available studies.

The funnel plot (Figure 3) displaying logit event rates of the individual studies versus the reciprocal of their standard errors showed no substantial asymmetry for studies that explored the effect of atropine on IHPS ($p = 0.28$ by the adjusted rank correlation test; $p = 0.45$ by Egger regression asymmetry test). Table 2 shows the evidence-based medicine (EBM) level and quality of the papers evaluated using the modified Jadad scale. The EBM level was based on the study design and the quality of each study. All papers were ranked as Level 4 evidence. For the quality of papers evaluated using the modified Jadad scale, five (45.5%) of 11 papers achieved a score of 4, three (27.3%) were awarded a score of 3, and three (27.3%) were given a score of 2.

4. Discussion

This meta-analysis shows that either oral or IV atropine sulfate was an effective treatment for IHPS in all but one study.

The etiology of IHPS remains unclear although several hypotheses have been postulated, including impaired function of acetylcholine and muscarinic receptors, decreased nitric oxide synthase activity, elevated prostaglandin and gastrin levels, infectious causes, and a genetic basis.[23—28] The mechanism of atropine sulfate in IHPS

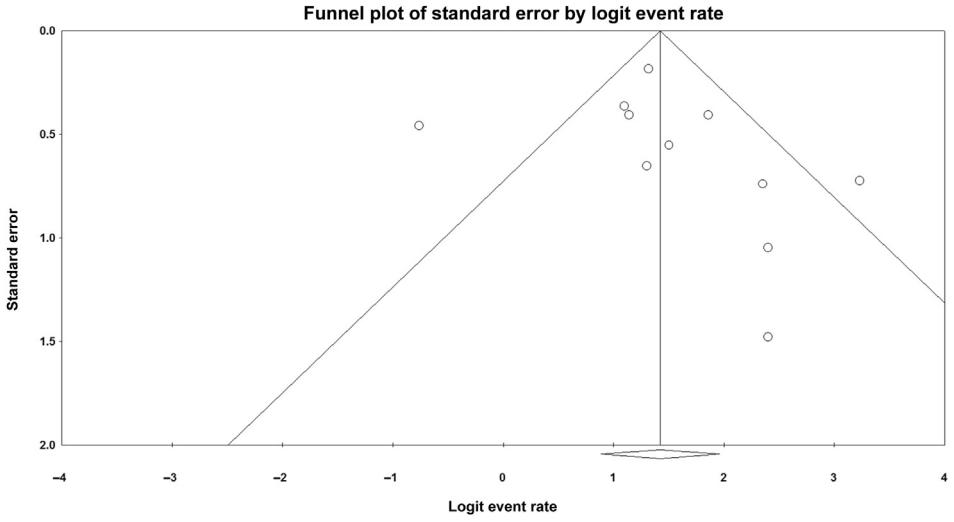

Figure 3 Funnel plot of standard error by logit event rate.

Table 2 EBM level and quality of papers evaluated by modified Jadad scale.

Study	EBM level	Blinding	Modified Jadad scale Score
Nagita A.[8]	4	No	3
Yamataka A.[12]	4	No	4
Riccabona M.[13]	4	No	3
Singh UK.[14]	4	No	3
Huang YC.[16]	4	No	2
Sretenovic A.[17]	4	No	2
Singh UK.[18]	4	No	2
Kawahara H.[19]	4	No	4
Meissner PE.[20]	4	No	4
Lukac M.[21]	4	No	4
Takeuchi M.[22]	4	No	4

The score for each article can range from 0 (lowest quality) to 8 (highest quality). Scores of 4–8 represent good to excellent (high quality) and 0 to 3 poor or low quality.

therapy mainly involves a cholinergic blocking agent with potent antimuscarinic activity that decreases peristaltic contractions by relaxing the pyloric smooth muscles.[29] The effective range varies widely, perhaps because of the alterations in the muscarinic receptor sensitivity of the muscle,[29] variations in drug clearance, compromised blood flow secondary to pyloric spasm, lack of nitric oxide synthase, and poor innervation of the pyloric circular musculature.[23,24,30]

The pharmacologic activity of IV atropine is 2–3 times greater than that of the oral form, with faster response to the effective IV dose. However, the IV form may be associated with more adverse effects, the most common of which are transient tachycardia and flushing. Oral atropine is absorbed from the intestines. Dilution with gastric contents and delayed emptying may prevent the desired amount reaching the intestines in the desired time. In this study, 70% of patients receiving oral atropine and 83.5% of patients receiving IV atropine initially followed by oral atropine benefitted from induced remission of IHPS. Initial IV atropine is more effective than oral atropine for treating IHPS despite the transient increase in serum ALT of 3.8–7.6%, which resolves without intervention. Mercer and Phillips[31] reported a success rate of 88% for conservative therapy with atropine in patients with IHPS. The result was gained from 10 studies pooled in a meta-analysis.[8,12–20] This study differed from our study in that the study of Kawahara et al[15] was not excluded and there was no statistical distinction between treatment with oral atropine only and initial IV atropine in the results.

Most studies show that vomiting ceases within 7 days, with earlier improvement than the time of normalization of the pyloric canal in medically treated groups. Singh et al[14] reported that vomiting ceased in 1–3 days, 4–7 days, and 9–12 days in patients with mild, moderate, and severe pyloric hypertrophy, respectively. However, the success rate was not different among the three groups, all of which received medical treatment. Kawahara et al[19] demonstrated a statistical difference in body weight (3885 g vs. 3230 g) at the time of presentation when comparing patients with successful and unsuccessful atropine therapy. However, Meissner et al[20] reported no difference in body weight at admission between these two groups. Pyloric canal normalization after treatment is evaluated by ultrasonography. Nagita et al[8] reported that time to normalization of pyloric muscle thickness ranged from 4 months to 12 months. Yamataka et al[12] reported that time to normalization of pyloric muscle thickness averaged 3.4 ± 2.3 months, with no significant difference in the pyloromyotomy group (3.8 ± 2.0 months), whereas Singh et al[14] reported 3–15 months after completion of oral therapy. Kawahara et al[15] reported that pyloric muscle thickness decreased significantly from 5 mm at presentation to 3 mm 3 weeks after completion of oral atropine treatment. In a report in 2004,[16] three of five patients receiving oral atropine had normalization of the pyloric canal in 35–47 days. In all of these reports, time to pyloric muscle normalization ranged from 5 weeks to 15 months for groups treated with atropine.

There were no adverse effects or complications related to the use of oral atropine in four studies. Thus, oral atropine is a simpler and safer treatment than IV atropine for treating IHPS. There are three reports[15,16,19] that used IV atropine for IHPS with a hospital stay of 13–14 days (13 days, 14.6 ± 6.2 days, and 13 days). Only one study[18] treated IHPS with oral atropine with a hospital stay of 1–2 days. Begg and Mazumdar[9] compared atropine and pyloromyotomy for managing IHPS and showed no difference in length of hospitalization, whereas three reports[20–22] cited prolonged hospital stay in the medical groups (12 days vs. 7 days in 2006, 8 days vs. 4 days, and 13 days vs. 8 days in 2013 for medical and surgical treatment, respectively).

In terms of costs, expenses were lower in the atropine group than in the pyloromyotomy group in one report.[12] However, in the studies of Kawahara et al[19] and Takeuchi et al,[22] the cost in medically treated cases was not significantly different than that in cases treated by pyloromyotomy alone because of the prolonged hospitalization in the medical cases.

This meta-analysis shows a strong tendency for successful treatment except in the report of Riccabona et al[13] (Figure 2), which had a 32% success rate for medical treatment. In this study, there was a difference in mean pyloric length of 15 mm in patients with successful medical treatment versus 18 mm in patients who underwent surgery. These findings can perhaps explain the low success rate in patients who received conservative treatment. However, the success rate increased to 77% in younger patients (age, <6 weeks). Thus, it is worthwhile to conduct atropine therapy in infants with IHPS prior to going directly to surgery. The standard process of meta-analysis is that articles should be extracted from randomized control trials. There were only three studies[12,21,22] that randomized patients into medical or surgical treatment for IHPS, and the cure rate of patients in surgical groups was 97–100%. Pyloromyotomy is no doubt a very effective treatment for IHPS and has a shorter length of stay in hospital than medical treatment. Surgical treatment is recommended in patients with severe dehydration and hematemesis, where medical treatment is inadequate. However, it is associated

with the risk of perforation of the stomach or duodenum, wound infection, wound dehiscence, and the risk of anesthesia, although these complications are infrequent. Future studies should focus on the randomization, growth rate, and neurodevelopment outcome between medically and surgically treated groups.

Although the current meta-analysis provided useful information, a potential limitation of this study is the quality of included studies, which varied from low to high. Only five of 11 papers[12,19–22] were of high quality (Jadad score, ≥4), whereas the other papers were of low quality. More high-quality studies are needed in the future. However, by performing sensitivity analyses that only included high-quality studies, the result was consistent with that obtained by pooling all available studies. It is unlikely that this shortcoming affected the findings.

In conclusion, medical treatment with either oral or IV atropine is a good alternative to pyloromyotomy for IHPS patients, particularly in infants with major concurrent disease or when parents are unwilling to let their infants undergo surgery. Oral atropine has less adverse effects than IV atropine for treating IHPS. Parents should be informed of this before they make their own decision.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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